Brain white-matter hyperintensities and treatment outcome in major depressive disorder

DAN V. IOSIFESCU, PERRY F. RENSHAW, IN KYOON LYOO, HO KYU LEE, ROY H. PERLIS, GEORGE I. PAPAKOSTAS, ANDERW A. NIERENBERG and MAURIZIO FAVA

Background  An increased incidence of brain white-matter hyperintensities has been described in major depressive disorder, but the impact of such hyperintensities on treatment outcome is still controversial.

Aims  To investigate the relationship of brain white-matter hyperintensities with cardiovascular risk factors and with treatment outcome in younger people with major depressive disorder.

Method  We assessed brain white-matter hyperintensities and cardiovascular risk factors in 84 people with major depressive disorder prior to initiating antidepressant treatment. We also assessed hyperintensities in 35 matched controls.

Results  We found no significant difference in the prevalence of white-matter hyperintensities between the depression and the control groups. Left-hemisphere subcortical hyperintensities correlated with lower rates of treatment response. We found no correlation between global hyperintensity measures and clinical outcome. Brain white-matter hyperintensities correlated with hypertension and age and with total cardiovascular risk score.

Conclusions  Subcortical white-matter hyperintensities in the left hemisphere (but not in other brain areas) may be associated with poor response to antidepressant treatment in major depression.

Declaration of interest  None.

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The association between major depressive disorder and increased prevalence of brain white-matter hyperintensities has been reported in elderly people (Krishnan et al, 1997; de Groot et al, 2000), but studies in younger patients have been inconclusive (Coffey et al, 1993; Lenze et al, 1999; Lyoo et al, 2002). In samples of elderly people with depression, such hyperintensities were associated with lower rates of response to antidepressant treatment (Hickie et al, 1997; Simpson et al, 1998; Stellens et al, 2002) as well as higher rates of relapse during follow-up (O’Brien et al, 1998; Yanai et al, 1998). The study reported here is, to our knowledge, the first to explore the impact of white-matter hyperintensities on antidepressant treatment outcome and the relationship between such hyperintensities and cardiovascular risk factors in younger people with depression. We predicted that the presence of brain white-matter hyperintensities would correlate with cardiovascular risk factors and with lower rates of treatment response.

METHOD

Participants  All study participants signed consent forms, approved by the institutional review board, prior to the initial study visit.

Non-treatment-resistant major depressive disorder  The study group with non-treatment-resistant major depressive disorder comprised 65 people aged 18–65 years (mean age 40.7, s.d. = 10.2), recruited through advertisements and clinical referrals for a clinical trial beginning with open-label fluoxetine treatment (Fava et al, 2002). All participants, 24 (37%) of whom were women, met criteria for major depressive disorder, diagnosed by the physician-administered Structured Clinical Interview for DSM–III–R Axis I Disorders – Patient edition (SCID–P; Spitzer et al, 1989).

Participants were required to have a score of 16 or over on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967) at the screening visit. We excluded people who failed to respond during the current episode of depression to at least one adequate antidepressant trial.

Treatment-resistant major depressive disorder  Nineteen participants (mean age 39.6 years, s.d. = 9.8), of whom 10 (52.6%) were women, were recruited at the Depression Clinical and Research Program at Massachusetts General Hospital for a clinical trial in people with treatment-resistant depression, beginning with open-label nortriptyline (Nierenberg et al, 2003). Patients eligible for inclusion were men and women aged 18–70 years with major depressive disorder diagnosed using the SCID–P and a score on the HRSD of at least 18. Treatment resistance was defined as non-response to at least one, but no more than five, adequate antidepressant trials during the current depressive episode.

Exclusion criteria  For both the depressive disorder samples, exclusion criteria were bipolar disorder, psychotic disorder, a history of organic mental or seizure disorder, serious or unstable medical illness, substance misuse or dependence disorder active within the past 12 months, acute suicidal risk, pregnancy, lactation, history of adverse reaction or allergy to the study medications, concomitant use of psychotropic medications, clinical or laboratory evidence of thyroid abnormalities, an existing diagnosis of dementia or a score below 27 on the Mini-Mental State Examination (Folstein et al, 1975), and any contraindication to magnetic resonance imaging, including metallic implants or severe claustrophobia.

Controls  We also recruited through advertisements 35 healthy volunteers, matched for age and gender (40% females; mean age 39.3 years, s.d. = 9.8). These volunteers underwent the physician-administered SCID–P to rule out any Axis I psychopathology.

Tests and procedures  We assessed cardiovascular risk factors in all participants with major depressive disorder following the National Institutes of Health Adult Treatment Panel III guidelines, based on the Framingham Heart Study (Wilson et al, 1998; Expert Panel
on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). We recorded, for each person in the two depression groups, age, gender, smoking status, family history of cardiovascular disease, total serum cholesterol, personal history of arterial hypertension and diabetes, and concomitant medications. We calculated a cumulated cardiovascular risk score (range 0–6) by assigning a point for each of the following six factors:

(a) age: male 45 years old or more, female 55 years old or more;
(b) active smoking status within the past 12 months;
(c) family history of premature vascular disease (e.g. myocardial infarction, stroke) in male first-degree relatives under 55 years old, and in female first-degree relatives under 65 years old;
(d) total cholesterol level greater than 5 mmol/l;
(e) arterial hypertension (blood pressure over 140/90 mmHg, or use of anti-hypertensive medication);
(f) diabetes mellitus.

After the initial evaluation the non-treatment-resistant sample entered 8 weeks of open-label treatment with fluoxetine 20 mg daily, following a 1-week wash-out phase. The HRSD was administered at each study visit (screen, baseline and then every other week for 8 weeks). The treatment-resistant group were prescribed nortriptyline at an initial dosage of 25 mg, which was increased by 25 mg per day until a dosage of 100 mg was reached, unless patients were unable to tolerate the dosage increase because of side-effects. Blood levels of nortriptyline were measured at weeks 2 and 6, and dosage adjustments were made after the second week if blood levels were below 400 nmol/l. Participants then maintained their dosage of nortriptyline for 6 weeks. The HRSD was administered at each study visit (screen, baseline and then weekly for 6 weeks).

Brain imaging procedures
All participants underwent brain magnetic resonance imaging using a 1.5T (Signa, General Electric, Milwaukee, Wisconsin, USA) whole-body imaging device. We obtained axial proton-density images, T2-weighted images (echo time TE=30/80 ms, repetition time TR=3000 ms, 256 × 192 matrix; field of view 24 cm, flip angle 45°, Nex value 0.5, 3 mm thick slices, no skip) and fluid-attenuated inversion recovery (FLAIR) axial images (TE=133 ms, TR=9002 ms, inversion time TI=2200 ms, 256 × 192 matrix; field of view 22 cm, 5 mm thick slices, 2 mm skip). Voxel dimensions were 0.975 mm × 0.975 mm × 3.0 mm. Analysis of the images was performed offline using a SUN Microsystems (Mountain-view, California, USA) Sparc2 workstation and the radiological film. Lesions were classified according to the Fazekas classification system (Fazekas et al, 1987), which provides an assessment of severity of the white-matter hyperintensities, rated separately for the subcortical white matter (range 0–3) and the periventricular white matter (range 0–3). The total white-matter hyperintensity score was considered to be the higher of the subcortical score and the periventricular score, following previous classifications of white-matter hyperintensity in people with major depressive disorder (Krishnan et al, 1997). All ratings of white-matter hyperintensities were done by an experienced neuroradiologist (H.K.L.), who was unaware of participant identity and clinical status. Another investigator in the study (D.V.L.) assessed independently a selection of 111 magnetic resonance images using the same rating criteria, for measurement of interrater reliability. This was very good: the number of observed agreements was 98 (88.3%) and weighted k=0.82.

The presence of severe hyperintensities was defined as a Fazekas scale score of 2 or over, whereas scores below 2 were categorised as not severe, following previous classifications in people with major depressive disorder (Krishnan et al, 1997). In addition to the Fazekas scale scores, we determined the localisation of hyperintensities by hemisphere (left or right). Subcortical hyperintensities were also localised as being in the frontal lobe or not in the frontal lobe area, using the central sulcus as a boundary.

Data analyses
The clinical outcome variables were response (reduction in HRSD score of 50% or more) and remission (final HRSD score of 7 or less). We analysed the clinical data using the last observation carried forward method. Group differences in demographic and clinical variables involving continuous data were computed using analysis of variance (ANOVA) (age) or unpaired t-tests (HRSD scores, percentage change in HRSD scores).

The differences in the severity of white-matter hyperintensities between participants in the two depression groups and the healthy comparison sample were analysed using χ²-tests. We used multiple ordinal logistic regression to test the association between hyperintensity scores and cardiovascular risk factors. Analysis of variance was used to test the association between hyperintensity scores and the total cardiovascular risk score (sum of the six cardiovascular risk factors). Since age is one of the cardiovascular risk factors, these analyses were not adjusted for age. Correlations between clinical outcome variables (response and remission) and hyperintensity scores were tested using logistic regression, adjusted for age. Statistical significance was defined as P<0.05, two-tailed.

RESULTS
The demographic and clinical characteristics of the three study groups are presented in Table 1. The initial HRSD scores for depression severity were not statistically different between the two depression groups: 21.6 v. 20.2; unpaired t-test, P=0.15.

The incidence of total brain white-matter hyperintensities in the group with non-treatment-resistant depressive disorder (63%) was not statistically different from that of the treatment-resistant group (53%) or the control group (60%); χ²=0.881, P=0.83. Also, the incidence of severe brain hyperintensities in the non-treatment-resistant group (8%) was not statistically different from that of the treatment-resistant group (5%) or the control group (6%); χ²=0.364, P=0.95. As expected, the individual’s age correlated with the severity of brain hyperintensities (ANOVA, d.f.=117, F=11.0, P=0.0012). In all three study groups the majority of subcortical hyperintensities were localised in the frontal lobe area: 87% of lesions in the treatment-resistant group were in the frontal lobe, 79% of lesions in the non-treatment-resistant group and 100% in the control group, with no statistically significant difference between groups (χ²=0.825, P=0.22).

White-matter hyperintensities and treatment outcome
After adjusting for age there was no statistically significant relationship between the
Clinical and demographic characteristics of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Treatment-resistant group (n=19)</th>
<th>Non-treatment-resistant group (n=65)</th>
<th>Healthy volunteer group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>39.6 (7.6)</td>
<td>40.7 (10.2)</td>
<td>39.2 (9.8)</td>
</tr>
<tr>
<td>Gender, female: n (%)</td>
<td>10 (53)</td>
<td>24 (37)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Cardiovascular risk score: mean (s.d.)</td>
<td>3.15 (1.22)</td>
<td>1.58 (1.21)</td>
<td></td>
</tr>
<tr>
<td>White-matter hyperintensity (WMH) score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WMH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WMH = 0</td>
<td>9 (47)</td>
<td>24 (37)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Total WMH = 1</td>
<td>9 (47)</td>
<td>36 (55)</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Total WMH = 2</td>
<td>0 (0)</td>
<td>4 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Total WMH = 3</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any WMH (WMH ≥ 1)</td>
<td>10 (53)</td>
<td>41 (63)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Severe WMH (WMH ≥ 2)</td>
<td>1 (5)</td>
<td>5 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Periventricular WMH (PWMH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWMH = 0</td>
<td>13 (68)</td>
<td>36 (55)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>PWMH = 1</td>
<td>6 (32)</td>
<td>27 (42)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>PWMH = 2</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PWMH = 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any PWMH (PWMH ≥ 1)</td>
<td>6 (32)</td>
<td>29 (45)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Severe PWMH (PWMH ≥ 2)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Deep (subcortical) WMH (DWMH)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWMH = 0</td>
<td>11 (58)</td>
<td>46 (71)</td>
<td>22 (63)</td>
</tr>
<tr>
<td>DWMH = 1</td>
<td>7 (37)</td>
<td>16 (25)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>DWMH = 2</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>DWMH = 3</td>
<td>1 (5)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any DWMH (DWMH ≥ 1)</td>
<td>8 (42)</td>
<td>19 (29)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Severe DWMH (DWMH ≥ 2)</td>
<td>1 (5)</td>
<td>3 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Left-sided DWMH</td>
<td>5 (26)</td>
<td>15 (23)</td>
<td>8 (23)</td>
</tr>
</tbody>
</table>

HRSD scores: mean (s.d.)

Baseline: 21.6 (3.2), 20.2 (3.8)
After treatment: 18.4 (5.1), 10.8 (7.3)
Percentage change in score: 0.14 (0.25), 0.48 (0.34)

Response, n (%): 1 (5), 35 (54)
Remission, n (%): 1 (5), 30 (46)

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Correlation between white-matter hyperintensities and cardiovascular risk factors

The white-matter hyperintensity score was significantly correlated with the cardiovascular risk score (Pearson r=0.37, P<0.05, Table 1). In a multiple ordinal logistic regression analysis examining individual cardiovascular risk factors, the white-matter hyperintensity score was significantly correlated with the cardiovascular risk score (Table 2).

<table>
<thead>
<tr>
<th>Lack of clinical response</th>
<th>Lack of clinical remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>χ²</td>
</tr>
<tr>
<td>Total WMH</td>
<td>0.36</td>
</tr>
<tr>
<td>Subcortical WMH</td>
<td>0.35</td>
</tr>
<tr>
<td>Left subcortical WMH</td>
<td>2.31</td>
</tr>
<tr>
<td>Right subcortical WMH</td>
<td>0.71</td>
</tr>
<tr>
<td>Periventricular WMH</td>
<td>0.04</td>
</tr>
</tbody>
</table>

OR, odds ratio; WMH, white-matter hyperintensity.
*P < 0.05
1. Response defined as a reduction in the score on the 17-item Hamilton Rating Scale for Depression of 50% or more.
2. Remission defined as final score of 7 or below on the Hamilton Rating Scale for Depression.
Table 3  Correlations between white-matter hyperintensities and cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Total WMH</th>
<th>Subcortical WMH</th>
<th>Periventricular WMH</th>
<th>Severe WMH³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANOVA</td>
<td>Ordinal logistic regression</td>
<td>ANOVA</td>
<td>Ordinal logistic regression</td>
</tr>
<tr>
<td></td>
<td>d.f.</td>
<td>F</td>
<td>P</td>
<td>Coef.</td>
</tr>
<tr>
<td>Total cardiovascular risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/gender (male ≥ 45, female ≥ 55)</td>
<td>1.79</td>
<td>4.50</td>
<td>0.037*</td>
<td>1.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.56</td>
<td>2.40</td>
<td>0.016*</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>1.01</td>
<td>3.20</td>
<td>0.001*</td>
<td>0.63</td>
</tr>
<tr>
<td>Family history of cardiovascular disease</td>
<td>0.99</td>
<td>1.65</td>
<td>0.098</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.03</td>
<td>0.01</td>
<td>0.99</td>
<td>-0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.57</td>
<td>0.62</td>
<td>0.53</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.97</td>
<td>1.94</td>
<td>0.053</td>
<td>0.15</td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; coef., coefficient; WMH, white-matter hyperintensity.
* P < 0.05
³ Fazekas score ≥ 2.
risk factors as predictors, greater total brain white-matter hyperintensity score was associated with age ($P=0.016$) and with hypertension ($P=0.001$). Two other cardiovascular risk factors did not reach statistical significance in relation to total hyperintensity score: cholesterol level ($P=0.053$) and family history of cardiovascular disease ($P=0.098$). The presence of diabetes and smoking status were not correlated with the total hyperintensity score. The presence of severe hyperintensities also correlated with age ($P=0.012$) and with hypertension ($P=0.041$), as well as with the total cardiovascular risk score ($P=0.011$).

The total cardiovascular risk score was correlated with the severity of periventricular hyperintensities ($P=0.008$) and of subcortical hyperintensities ($P=0.047$). In a multiple logistic regression, the severity of periventricular hyperintensity correlated with age ($P=0.023$) and hypercholesterolaemia ($P=0.017$), whereas hypertension did not reach statistical significance ($P=0.088$). Hypertension also did not reach statistical significance in relation to subcortical hyperintensities ($P=0.078$). Other cardiovascular risk factors did not correlate with the severity of periventricular or subcortical white-matter hyperintensities.

**DISCUSSION**

This is to our knowledge the first study investigating the impact of brain white-matter hyperintensities on antidepressant treatment outcome in a non-geriatric study sample. There are several important findings in this study. First, although we found no correlation between global white-matter hyperintensity measures and clinical outcome, subcortical hyperintensities in the left hemisphere were associated with poor outcome of antidepressant treatment. Previous studies in geriatric populations have described an association between subcortical and basal ganglia white-matter hyperintensity (and not periventricular hyperintensity) and poor treatment outcome in major depressive disorder (Hickie et al., 1997; O’Brien et al., 1998; Simpson et al., 1998; Steffens et al., 2002). However, to our knowledge there is no other report indicating a differential impact of left-hemisphere subcortical white-matter hyperintensity on treatment outcome in major depressive disorder. Further studies will be needed to validate this association. Our finding is consistent with the report of Greenwald et al. (1998), in which left frontal subcortical white-matter lesions significantly correlated with the diagnosis of major depression. Also, previous reports in post-stroke depression have indicated left-sided frontal lobe lesions as predictors of severity of depression at 3 months and 6 months after the stroke (Robinson et al., 1985); left frontal localisation of stroke was not predictive of depression at long-term follow-up (Shimoda & Robinson, 1999). However, this pattern would be consistent with the results we are reporting here, as only short-term, acute-phase treatment outcomes were measured in our study.

A second important finding in our study was that brain white-matter hyperintensities were correlated with cardiovascular risk factors in non-elderly people with major depressive disorder. It is therefore possible that a large proportion of brain hyperintensities in this younger population might be vascular in origin. Our result is consistent with findings in non-psychiatric populations, where brain white-matter hyperintensities have been associated with age, cerebrovascular disease (Awad et al., 1986; Fazekas et al., 1993) and cardiovascular risk factors such as smoking, arterial hypertension and increased serum cholesterol (Breteler et al., 1994; Liao et al., 1997; Schmidt et al., 1997). In neuropathological analyses of brains from people with major depressive disorder, subcortical white-matter hyperintensities were all ischaemic (Thomas et al., 2002), whereas periventricular lesions had multiple causes (Thomas et al., 2003).

One possible interpretation of our results is that cardiovascular risk factors correlate with a higher severity of subcortical white-matter lesions, which in turn correlates with poor treatment outcome in depression. This interpretation would be consistent with the ‘vascular depression’ model. However, the vascular depression hypothesis would call for a higher prevalence of hyperintensities in patients with depression compared with normal controls, which was not found in our study. Also, the vascular depression model would suggest a relationship between global measures of brain white-matter hyperintensities and treatment outcome, whereas in our sample only subcortical hyperintensities in the left hemisphere (and no other hyperintensities) were associated with poor response to antidepressant treatment. Other factors, such as disruption by white-matter hyperintensities of specific white-matter tracts involved in mood regulation, may explain our observed result of a selective impact of left-hemisphere subcortical hyperintensities on treatment outcome. Other predictors of treatment outcome, which may mediate the relationship between white-matter hyperintensity and treatment response, might have been missed in this study owing to the relatively small sample size.

There are several limitations to our study. First, we used a whole-brain rating scale (Fazekas et al., 1987) to assess the severity of brain white-matter hyperintensities. Although most studies on this topic reported using modified versions of the Fazekas scale, this method does not allow for a detailed morphological and volumetric analysis of brain white-matter hyperintensity (Taylor et al., 2003). We did not measure hyperintensity localisations such as basal ganglia, which have been previously described as associated with treatment outcome in major depressive disorder (Simpson et al., 1998). Second, we measured only total cholesterol and not fractions of cholesterol, therefore our results may not reflect the full impact of this cardiovascular risk factor. Third, we have a potential sampling bias, as we enrolled participants from two antidepressant trials with specific inclusion and exclusion criteria and with different treatments (fluoxetine and nortriptyline); as a result, this sample may not directly reflect the typical out-patient population.

**ACKNOWLEDGEMENTS**

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Schmidt, R., Fazekas, F., Hayn, M., et al. (2001) Cerebrovascular disease and evolution of depressive symptoms in the left hemisphere were associated with poor response to antidepressant treatment in major depressive disorder, but we found no correlation between global white-matter hyperintensity measures and clinical outcome.

In younger people with major depressive disorder, the presence of such hyperintensities was associated with cardiovascular risk factors (hypertension and age) and with the total cardiovascular risk score.

We found no difference in the prevalence or distribution of white-matter hyperintensities between healthy volunteers and two groups of younger people with depression (treatment-resistant and non-treatment-resistant).

**CLINICAL IMPLICATIONS**

- Subcortical white-matter hyperintensities in the left hemisphere were associated with poor response to antidepressant treatment in major depressive disorder, but we found no correlation between global white-matter hyperintensity measures and clinical outcome.

- In younger people with major depressive disorder, the presence of such hyperintensities was associated with cardiovascular risk factors (hypertension and age) and with the total cardiovascular risk score.

- We found no difference in the prevalence or distribution of white-matter hyperintensities between healthy volunteers and two groups of younger people with depression (treatment-resistant and non-treatment-resistant).

**LIMITATIONS**

- We cannot exclude significant effects of white-matter hyperintensities in specific brain regions not examined here.

- We cannot assess the role of fractions of cholesterol (important cardiovascular risk factors), as only total cholesterol was measured.

- We enrolled participants from two separate antidepressant trials, using different treatments (fluoxetine and nortriptyline).

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